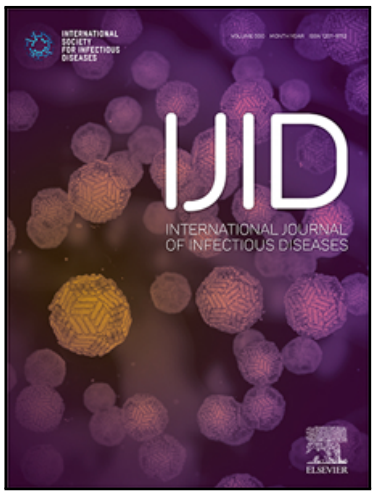
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



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Highlights

- Early cardiac pathology likely caused by vasoconstriction ischemia then anoxia
- Ischemia and anoxia possibly caused by vasoconstriction of cardiac pericyte cells
- Vasoconstrictions likely caused by histamine or SARS-CoV-2 pericyte infection

Models for COVID-19 Early Cardiac Pathology Following SARS-CoV-2 Infection

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Highlights

- Early cardiac pathology likely caused by vasoconstriction ischemia then anoxia
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Keywords

- Myocarditis, SARS-CoV-2, COVID-19, mast cell disease, cardiac pathology

Abstract

Objectives: The clinical manifestations of COVID-19 associated cardiac complications are heterogeneous, ranging from asymptomatic to severe symptoms including arrhythmias and cardiogenic shock. For COVID-19 patients with cardiac sequela, only a small subset of patients have myocarditis; the pathogenesis of cardiac sequela caused by SARS-CoV-2 other than microthrombi associated sequela remains to be determined.

Methods: Retrospective analysis of 71 heart autopsy specimens from COVID-19 and putative COVID-19 in the NIH COVID Digital Pathology Repository.

Results: The most consistent observation was that of localized myocardial cell death not associated with either myocarditis or microthrombi. Red blood cells were typically absent from capillaries, but when observed were predominately in linear clusters (stacks) of adjacent cells.

Conclusions: Based on our retrospective analysis, we propose that localized ischemia and subsequent cell death by anoxia contributes to the cardiac pathogenesis in some COVID-19 patients. We propose two new models predicting vasoconstriction of cardiac pericyte cells induced by elevated histamine from hyper-activated mast cells or by direct infection. We propose that impeded blood flow and cell death by anoxia are initial steps in the development of SARS-CoV-2 induced cardiac injury in COVID-19 patients independent of microthrombi or myocarditis.

Introduction

The SARS-CoV-2 virus causing the COVID-19 pandemic is an airborne respiratory virus that directly infects cells expressing the ACE2 protein. Clinical COVID-19 expression varies widely from asymptomatic to severe (He Guiqing et al., 2020, Hu et al., 2020, Mizumoto et al., 2020, Tian et al., 2020). While individual symptoms vary, fairly consistent patterns of disease are observed, including cardiovascular complications such as myocarditis. The clinical manifestations of cardiac complications are heterogeneous, ranging from asymptomatic to severe symptoms including arrhythmias and cardiogenic shock. For COVID-19 patients with cardiac sequela, only a small subset of patients have myocarditis (Basso et al., 2020, Bearse et al., 2021); the pathogenesis of cardiac sequela caused by SARS-CoV-2 remains to be determined.

Clinical observations provide some insights into COVID-19 associated sequela. Preexisting cardiovascular disease (CVD) is common in COVID-19 patients and associated with unfavorable outcomes (Li et al., 2020); patients with CVD were older (62 vs 52 years) and had a higher mortality rate (16.7% vs. 4.7%) than those without CVD (Li et al., 2020). A common cause of COVID-19 associated cardiac sequela are microthrombi (Rapkiewicz et al., 2020). A meta-analysis of observational studies found 14.1% of 77,317 hospitalized COVID-19 patients had cardiovascular symptoms or complications (angina, arrhythmias, myocardial injury, acute heart failure or myocardial infarction) (Sabatino et al., 2020). A study of 784 COVID-19 patients found arrhythmia in 48% of patients with poor outcome and 6% in patients without poor outcome (Pranata et al., 2020). A retrospective study of 150 COVID-19 patients found myocardial damage in 18% of the fatal cases of which 14.7% also had circulatory failure (Ruan et al., 2020). Myocarditis was observed in a subset of patients with severe COVID-19 (Bernal-Torres et al., 2020, Beşler and Arslan, 2020, Doyen et al., 2020, Sala et al., 2020). Though

cardiac injury is common among infected patients, evidence of myocarditis appears in 7.2% COVID-19 autopsies with less than 2% functionally significant (Halushka and Vander Heide, 2021). COVID-19 associated cardiac sequela appears like myocarditis without associated infiltration of immune cells in the majority of the patients.

Clinical laboratory measurements in COVID-19 patients with cardiac sequela are indicators of ongoing damage and death of cardiomyocytes. In COVID-19 patients, elevated troponin I level is a biomarker of cardiac injury (Guo et al., 2020, Nie et al., 2020, Shi et al., 2020). In a study of 309 COVID-19 patients, overall mortality was significantly higher in the patients with elevated troponin I (n=116, 37.9% vs. 11.4%, odds ratio: 4.45, P<0.001) (Shah et al., 2020). Similarly, an additional study with serum troponin assessment examined 6,247 COVID-19 patients and found 15% had mildly elevated and 14% had severely elevated troponin levels with significantly increased odds of death (odds ratio: 2.06, p<0.001 for mildly elevated and odds ratio: 4.51, p<0.001 for severely elevated) (Majure et al., 2021). Moreover, a multicenter study in Italy of 614 COVID-19 patient reports 45% had elevated troponin (T or I) levels associated with increased in-hospital mortality (37% vs 13%, p=0.01) (Lombardi et al., 2020). Elevated troponin levels indicate myocyte cell death. Cardiomyocytes do not express the ACE2 receptor used by the SARS-CoV-2 virus.

Evidence of SARS-CoV-2 infection of the heart is limited. A study of autopsies of 21 consecutive COVID-19 patients found lymphocytic myocarditis in 14%, a mild pericarditis in 19%, and increased interstitial macrophage infiltrate present in 86% of cases (Basso et al., 2020). SARS-CoV-2 infection of macrophages and rare endothelial cells were found in 30 of 41 (73%) consecutive fatal COVID-19 autopsies with only 4 (9.7%) cases of myocarditis (Bearse et al., 2021). Likewise, Tavazzi et al. found infected macrophages in the heart (Tavazzi et al., 2020).

A model for SARS-CoV-2 infecting macrophage via Fc receptor uptake of antibody bound virus has been previously proposed (Ricke, 2021). Understanding cardiac sequela in COVID-19 patients can lead to improved treatments.

Based on our retrospective analysis of heart autopsy specimens from patients with COVID-19 or putative COVID-19 in the NIH COVID Digital Pathology Repository, we propose that COVID-19 associated cardiac pathogenesis is caused by localized ischemia and subsequent cell death by anoxia. We propose two models for the initial steps of cardiac pathogenesis associated with COVID-19. These two models involve cardiac capillary vasoconstriction by activated pericytes.

Model 1 follows the prediction of COVID-19 being a mast cell disease (Afrin et al., 2020, Malone et al., 2021, Theoharides, 2021) (Figure 1). We predict the SARS-CoV-1 and SARS-CoV-2 nucleocapsid proteins upregulate COX-2 by binding to the promoter resulting in elevated prostaglandin E2 (PGE_2) levels (Tomera Kevin et al., 2020, Yan et al., 2006). Elevated levels of PGE2 can cause hyper-activation of mast cells, leading to degranulation and release of inflammatory mediators such as histamine (Morimoto et al., 2014). This hypothesis was previously proposed to occur in COVID-19 patients (Tomera Kevin et al., 2020). Moreover, pericytes can react to histamine (Sims et al., 1990) and elevated histamine levels are associated with the contraction of pericytes and endothelial cells (Hamilton et al., 2010, Kelley et al., 1988) resulting in impeded blood flow through capillaries. Contracted pericytes also impede cerebral blood flow leading to ischemic events (Attwell et al., 2016). This model predicts pericyte capillary vasoconstrictions resulting in localized myocyte cell death by anoxia.

Model 2 proposes that SARS-CoV-2 directly infects pericytes causing vasoconstriction (Figure 1). Pericytes express ACE2 (He Liqun et al., 2020, Xu et al., 2021, Zhou et al., 2020,

Ziegler et al., 2020). A previously proposed model of cross-linked red blood and endothelial cells by SARS-CoV-2 binding to CD147 protein is also consistent with our histology observations (Scheim, 2020); impeded blood flow and cell death by anoxia is possible from "clumps" of cross-linked red blood cells (Scheim, 2020). Herein, we propose that COVID-19 associated cardiac pathogenesis is initiated by vasoconstriction caused by constricted pericytes leading to impeded blood circulation and myocyte cell death by anoxia.

Results

The NIH COVID Digital Pathology Repository provides 71 numbered digital cardiac images: 1-2, 5, 7-9, 25-35, 37-63, 65-90, and 92 of COVID-19 and putative COVID-19 patient autopsies (Hewitt et al., 2020). In this retrospective analysis of these heart autopsy specimens, we observed localized regions of myocytes with degenerate or absent nuclei consistent with individual cell necrosis, without cellular infiltration by immune cells. The majority of cardiac capillaries were devoid of red blood cells. When observed, red blood cells were seen in clusters in short segments of residual intact capillaries.

Discussion

In our retrospective analysis of heart autopsy specimens from patients with COVID-19 or putative COVID-19 in the NIH COVID Digital Pathology Repository (Hewitt et al., 2020), we observed localized regions of myocytes with degenerate or absent nuclei consistent with individual cell necrosis, without evidence of cellular infiltration by immune cells (myocarditis). This pattern of histological evidence illustrates cell distress and death. We propose the lack of

observed immune cells in response to cell death likely results from impeded blood flow to impacted cardiac regions.

We present two new hypotheses for the observed cardiac pathology. The first hypothesis is that some pericytes are activated following histamine release from hyper-activated mast cells (Ricke et al., 2020). The second hypothesis is that pericytes are infected by SARS-CoV-2, resulting in constriction and clamping of the pericyte. Both of these models are consistent with SARS-CoV-2 infected macrophages observed in heart autopsies (Bearse et al., 2021, Tavazzi et al., 2020) resulting in activated mast cells releasing histamine or infected pericytes. Constricted pericytes impede blood flow through capillaries with subsequent cell death by anoxia (Ricke et al., 2020). The third model consistent with the histology observations was proposed by David Scheim for "clumps" of cross-linked red blood cells impeding blood circulation (Scheim, 2020). These three models are consistent with the observed histological evidence including a combination of two or all three models. Impeded blood flow and cell death by anoxia may be the cause of cardiac manifestations and abnormal myocardial measures detected by standardized CMR observed in SARS-CoV-2 infected individuals (Puntmann et al., 2020, Rajpal et al., 2021, Starekova et al., 2021). These models could explain cardiac manifestations including death for patients recovering from COVID-19; example sudden cardiac death of 65 year old woman recovering from mild COVID-19 (Yao et al., 2020).

Based upon the observation of cardiac changes in asymptomatic individuals, impeded capillary circulation may be a risk factor for individuals infected by SARS-CoV-2. In addition to COVID-19, it is proposed that hyper-activated mast cells and elevated histamine levels may contribute to the pathophysiology of COVID-19 induced multisystem inflammatory syndrome in

children (MIS-C) and adults (MIS-A), and Kawasaki Disease which can lead to adverse cardiac sequalae (Ricke et al., 2020).

A set of therapeutic agents targeting the mast cells and COX-2 exhibit efficacy in COVID-19 patients (Blanco et al., 2021, Hogan Ii et al., 2020, Malone et al., 2021, Samimagham et al., 2020). The success of these therapies provides indirect support for our proposed pericyte hypotheses that suggest either hyper-activated mast cells release histamine or SARS-CoV-2 infected pericytes cause vasoconstriction. In an experimental viral myocarditis mouse model, treatment with cetirizine, a histamine H1 receptor antagonist, improved survival, lung congestion, myocardial necrosis, and suppressed expression of pro-inflammatory cytokines (Matsumori et al., 2010). These results suggest that histamine released from mast cells may play a pivotal role in viral cardiac pathogenesis. A retrospective study of patients with chronic heart failure (CHF) revealed treatment with famotidine, a histamine H2 receptor antagonist, improved both cardiac symptoms and ventricular remodeling associated with CHF (Kim et al., 2006). A set of H1 receptor antihistamines including cetirizine, dexchlorpheniramine, loratadine, and ebastine combined with azithromycin exhibit efficacy in COVID-19 patients (Blanco et al., 2021). High dose famotidine (Janowitz et al., 2020, Malone et al., 2021) also exhibits evidence of efficacy in COVID-19 patients (Chow et al., 2021b, Tomera Kevin et al., 2020, Tomera Kevin M. et al., 2020). Combination therapy to target the H1 receptor on mast cells with Cetirizine and the H2 receptor with famotidine also shows evidence of efficacy in COVID-19 patients (Hogan Ii et al., 2020). Moreover, treatment with high dose celecoxib to target the upregulated COX-2 enzyme shows evidence of efficacy (Hong et al., 2020) as sole therapy and in combination with high dose famotidine (Chow et al., 2021b, Tomera Kevin et al., 2020, Tomera Kevin M. et al., 2020). Montelukast, a leukotriene receptor antagonist, appears to demonstrate clinical utility in

COVID-19 patients (Khan et al., 2021). Aspirin exhibits efficacy in COVID-19 patients (Chow et al., 2021a, Mura et al., 2021, Osborne et al., 2021); while the mode of action in COVID-19 patients is unknown, aspirin is known to stabilize mast cells, target COX-2, and anti-coagulate. In Long COVID patients (n=25), 53.8% with chest pain experienced reduction or resolution of symptoms when treated with histamine receptor H1 antagonists loratidine or fexofenadine and H2 antagonists famotidine or nizatidine (Glynne et al., 2021). The efficacy of these treatments provides potential support for the models proposed. We propose that these treatments likely reduce or minimize cardiac pathology associated with COVID-19.

Conclusion

In our retrospective analysis of heart autopsy specimens from patients infected with SARS-CoV-2, we observed histopathological evidence of myocyte necrosis without cellular infiltration by immune cells. These observations are consistent with the hypothesis that COVID-19 cardiac pathology is initiated by impeded capillary circulation, and associated cell death by anoxia. SARS-CoV-2 associated cardiac pathology may be reduced or preventable with treatments targeting the histamine pathway that exhibit efficacy in treating COVID-19 patients.

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Author Contribution

MF-S, PT, DR, and NS contributed to conception and design. MF-S, PT, and DR contributed to retrospective histology review. DR and NG to drafting the manuscript; and all authors to critically revising the manuscript. All authors read and gave final approval to the final manuscript.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical Approval Statement

Ethical approval was not required because this was a retrospective analysis of publicly available deidentified autopsy images.

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Figures

Figure 1. Two models for COVID-19 Early Cardiac Pathology Following SARS-CoV-2 Infection. Model 1 proposes that histamine released from activated mast cells induces constricted pericyte vasoconstrictions and localized tissue ischemia followed by myocyte anoxia. Model 2 proposes vasoconstrictions associated with SARS-CoV-2 infected cardiac pericytes resulting in localized tissue ischemia and myocyte anoxia.